

Establishment Inspection Report

Bayer Healthcare Pharmaceuticals Inc.
Whippany, NJ 07981-1544

FEI: 2243252
EI Start: 8/3/2018
EI End: 8/9/2018

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SUMMARY

This routine surveillance Risk Evaluation and Mitigation Strategies (REMS) inspection of Bayer Healthcare Pharmaceuticals Inc. was initiated as requested by the Center for Drug Evaluation and Research (CDER) as per assignment memorandum dated 19 Dec 2017 (**Attachment 1**). FACTS Assignment # 11780000; eNSpect OP ID # 88751. This assignment was conducted to assess the firm's compliance with the applicable regulations and in accordance to CP 7353.001 (Risk Evaluation and Mitigation Strategies (REMS) Reporting Inspections).

The previous inspection was a sponsor inspection. It was conducted between 19 Jun 2017 and 27 Jun 2017 and classified NAI.

The current inspection covered the application NDA 204819. I reviewed training records, audit plans, standard operating procedures, Prescriber and Pharmacy Guide, Medication Guides, Guide for Females who can get pregnant.

On 9 Aug 2018, a closeout meeting was held and no Form FDA-483, *Inspectional Observations*, was issued.

No refusals were encountered. No samples were collected.

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ADMINISTRATIVE DATA

Inspected firm: Bayer Healthcare Pharmaceuticals Inc.
Location: 100 Bayer Blvd
Whippany, NJ 07981-1544
Phone: 826-404-3000
FAX: 862
Mailing address: 100 Bayer Blvd, Po Box 915
Whippany, NJ 07981-1544
Email address:
Dates of inspection: 8/3/2018, 8/6/2018-8/7/2018, 8/9/2018
Days in the facility: 4
Participants: **Shirley S Wen, Investigator**

On 3 Aug 2018, I, Investigator Wen, presented my credentials and issued a Form FDA-482, *Notice of Inspection (Attachment 2)*, to Dario F. Mirski, M.D., Senior Vice President and Head of Medical Affairs. During the opening meeting, I was informed that they changed their firm name to Bayer U.S. LLC. Upon further discussion, they revealed that they were wrong. According to Daniel C. Ricci, *Director of Quality Strategy and Inspection Intelligence*, Bayer U.S. LLC is used only for the purpose of platforming employees in the U.S. for benefits and Human Resource requirements. However, Bayer Healthcare Pharmaceutical Inc. is still their legal firm name that is used for all business-related activities.

On 9 Aug 2018, I held a closeout meeting with Dario F. Mirski, M.D and the management team. No Form FDA-483, *Inspectional Observations*, was issued.

The entire report was written by FDA Investigator Shirley Wen. Throughout this report, Bayer Healthcare Pharmaceuticals Inc. may be referred to as "Bayer."

All FDA correspondence should be sent to:
Joseph Quintavalla, Deputy Director of Global Regulatory Strategist
100 Bayer Boulevard
Whippany, NJ 07981 - 0915

HISTORY

Dr. Dario F. Mirski provided an opening PowerPoint presentation of the current Bayer organizational structure and Adempas (NDA 204819) REMS Program. I obtained a copy of the PowerPoint slides from the opening presentation (**Exhibit 1, 2**). Bayer currently only has one REMS program. Adempas REMS was approved by the FDA on 8 Oct 2013 and the program started

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operating on 8 Oct 2013. The product was first commercially available on 10 Oct 2013.

Mr. Daniel Ricci stated that there are approximately (b) (4) employees worldwide and a total of (b) (4) employees at this current location in Whippany, NJ. Bayer's normal hours of operation at this facility are between (b) (4) .

JURISDICTION (PRODUCTS MANUFACTURED AND/OR DISTRIBUTED)

This inspection covered Adempas REMS program (NDA 204819). Adempas REMS program started operating on 8 Oct 2013.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED**Dario F. Mirski, M.D., Senior Vice President and Head of Medical Affairs**

Mr. Mirski is the head of the Medical Affairs Department in the U.S. and the Americas. He joined Bayer 4 years ago. He has responsibility over the Medical Affairs Therapeutic Areas, data generation and observational studies, and medical information. He was present during the opening and closeout meeting. He reports to Michael DeVoy, M.D., *Head of Medical Affairs and Pharmacovigilance and Chief of Medical Officer Bayer AG*.

Daniel C. Ricci, Director of Quality Strategy and Inspection Intelligence

Mr. Daniel Ricci facilitated this inspection and provided the requested documents and copies throughout the inspection. He joined Bayer (b) (6) . He provides leadership for sponsor Good Clinical Practice and Pharmacovigilance related inspections, as well as investigator GCP site inspections. He reports to Andy Hargreaves, *Head of Quality Strategy and Inspection Intelligence*.

Joseph Silverman, Associate Director of U.S Medical Affairs for Phase IV Clinical Trials

Mr. Silverman was present throughout the inspection and provided requested information and documents. He joined Bayer (b) (6) . He manages REMS operations to ensure compliant implementation of the REMS program including the monitoring and verification of task completion. He also reviews and finalizes REMS documentation and provides status reports to management. He reports to Anneliese LaRose, *Director of U.S. Medical Affairs for Phase IV Clinical Trials*.

The following individuals were also present during the opening meeting:

- Alexandra Vlajnic, *Vice President of U.S. Medical Affairs of General Medicine/Hematology and Dermatology*
- Donato Silvestri, *Deputy Director of Compliance and Audit Management, U.S. Medical Affairs*
- Hong Sajonz, *Deputy Director of Compliance and Audit Management, U.S. Medical Affairs*
- Gregory M. Longest, *Director of Compliance Training and Operations, U.S. Pharmacovigilance*
- Carina Goldberg, *Deputy Director of Local Safety Manager, U.S. Pharmacovigilance*

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- Bernarda Alarcon-Setti, *Global Inspection Manager of Quality Strategy and Inspection Intelligence*
 - Larry Thomas, *Senior Global Systems Auditor of System Audit Management*
- Joseph Quintavalla, *Deputy Director of Global Regulatory Strategist*

FIRM'S TRAINING PROGRAM

According to Mr. Silverman, Bayer trained designated personnel at each out-patient pharmacy on how to handle Adempas medication and Adempas REMS Procedures. These individuals then trained the other personnel at their pharmacies on these procedures. Bayer would retrain the pharmacy if it was necessary. During annual audits, auditors from Bayer would review the training logs. Bayer did not perform training at inpatient pharmacies. Inpatient pharmacies conducted self-training by reviewing all Adempas REMS related materials and then submitting the Inpatient Pharmacy Enrollment Form (**Exhibit 3**). The form can be found on the website www.adempasREMS.com.

MANUFACTURING/DESIGN OPERATIONS

According to Mr. Racci, there are a total of (b) (4) inpatient pharmacies enrolled and a total of (b) (4) are currently active. There is a total of (b) (4) active out-patient pharmacies. They use the (b) (4) REMS database for the Adempas REMS program. I collected the database validation certificate (**Exhibit 4**).

Contractors

The following contractors were used in the REMS program:

(b) (4)

Out-patient selection and audit

According to Mr. Silverman, (b) (4) were selected by the commercial teams based on the following criteria:

(b) (4)

(b) (4) was selected by the commercial teams as they are a very large regional payer/HMO in the (b) (4) that was growing. They have a large number of PH patients under their care.

According to Mr. Silverman, they perform out-patient pharmacy audits in between (b) (4). They have finished the audits for the year of 2018. I collected a list of 2018 audit status for out-

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patient pharmacies and a list for 2016 and 2017 (**Exhibit 5, 6**). Due to Bayer's policy, I was not able to review the audit reports. I reviewed the audit summary for 2017. There were no critical observations noted during the audits in 2017. They did not have a summary for 2016. According to Mr. Racci, a REMS assessment report was not required prior to 2017; therefore, they did not have a summary of audit findings before 2017.

These out-patient pharmacies were audited annually. According to Mr. Racci, Bayer does not do cross analysis on the findings identified during the audits. Therefore, they could not provide an answer of if any repeated issues occurred. However, they have a new audit plan every year based on what they found from previous audits. I reviewed the audit plans for 2016, 2017 and 2018. I did not identify any deficiencies.

According to Mr. Silverman, there was 1 incidence of Adempas distribution to a non-certified inpatient pharmacy. (b) (4) a Certified Specialty Distributor (CSD), dispensed 2 shipments on 6 Jan 2016 and 1 shipment on 11 Jan 2016 to a non-certified inpatient pharmacy. The root cause was the CSD shipped drug to a non-certified Pharmacy due to incorrect guidance from Coordinating Center Associate (CCA). The following actions were taken for this incidence:

- Re-trained CCA and CCA developed a call script for CSD to use when calling in to verify enrollment and eligibility of the Inpatient Pharmacies
- This non-certified Inpatient Pharmacy enrolled into Adempas REMS program on 14 Jan 2016.
- CSD was re-educated

According to Mr. Silverman, (b) (4) monitors outpatient prescriptions on a daily basis to confirm REMS requirements are being met and Health Care Professionals (HCPs) are certified. Bayer and (b) (4) also have an escalation process in place to review any issues that may arise in real time. Specialty Pharmacy (SP) Communication Flow, SP Exception Review Flow, and SP Restatement Review Flow were provided by Bayer (**Exhibit 7**). All compliance events are also reviewed on a quarterly basis at the CCA meeting.

In-patient audit

Audit

According to Mr. Silverman, they audit (b) (4) of their inpatient pharmacies every year. The pharmacies were selected based on their activities. I collected a list of inpatient pharmacies audit dates for 2016 to 2018 (**Exhibit 8, 9**).

Additional information

According to Mr. Silverman, there were no critical issues that necessitated implementing a Corrective and Preventive Action (CAPA). (b) (4) reviews the specialty pharmacy shipment data daily to review for any non-compliance events. Per the compliance plan, (b) (4) provides Bayer Operation metrics (b) (4) for Bayer to review and monitor how many Females of Reproductive Potential (FRP) were dispensed greater than a 30 day supply from an out-patient pharmacy without an

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override. There were 11 shipments where a supply of more than 30 days was dispensed to an FRP from out-patient pharmacies. All cases requiring more than a 30 day supply of Adempas treatment have to be authorized by a Health Care Professional (HCP); however, the HCP is not required to provide a reason. There were 11 cases where more than a 30 day supply was dispensed. For 10 of these cases, a HCP authorized dispensing of greater than a 30 day supply; there were five shipments without an accompanying reason and five shipments with reasons. The remaining one shipment was due to a dispensing error.

According to the document Mr. Silverman provided, the inpatient pharmacy would dispense no more than a 15 day supply of Adempas to patients upon discharge from the healthcare facility. During Bayer's annual audits of the Inpatient Pharmacies, Bayer auditors review the dispensing data for female patients provided Adempas upon discharge.

There are ^{(b) (4)} pregnancy cases reported with Adempas use between 10 Oct 2013 to 7 Aug 2018 across the country.

There was one case that Adempas was prescribed to a non-enrolled female patient. The medication was dispensed to the patient on 29 Jan 2016. The corrective action of this case was to enroll this female patient, and the preventive action for this case was to re-train the pharmacy on the Adempas REMS requirements (conducted on 24 Feb 2016).

REFUSALS

No refusals were encountered.

GENERAL DISCUSSION WITH MANAGEMENT

On 9 Aug 2018, I held the closeout meeting with Dario F. Mirski, M.D and the management team. No Form FDA-483, *Inspectional Observations*, was issued.

EXHIBITS COLLECTED

- 1 Presentation of the Company, 15 pages
- 2 Presentation of the Adempas REMS Program, 9 pages
- 3 Inpatient Pharmacy Enrollment Form, 1 page
- 4 REMS Database Validation Certificate, 1 page
- 5 2018 Out-Patient Pharmacy Audit, 2 pages

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- 6 2016 and 2017 Out-Patient Pharmacy Audit, 1 page
- 7 Flow Chart, 5 pages
- 8 2016 and 2017 Inpatient Pharmacy Audit Dates, 1 page
- 9 2018 Inpatient Pharmacy Audit Dates, 1 page

ATTACHMENTS

- 1 Assignment Memorandum, 11 pages
- 2 Form 482, 3 pages

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9/28/2018

X Shirley S Wen

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Signed by: PIV

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